Evaluation of a care pathway for patients with long-term pain after knee replacement

Health Economic Analysis Plan

Version 1.0 (05/06/2020)

Contents

Section 1: Administrative information

1.1 HEAP administrative information

Title	Health Economics Analysis Plan (HEAP) for a randomised controlled trial of the STAR programme. A multi-centre randomised controlled trial to evaluate a care pathway for patients with long-term pain after knee replacement.
Trial registration number; registry	ISRCTN registry (ISRCTN92545361), prospectively registered on 30 August 2016.
Source of funding	National Institute for Health Research (NIHR) Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol.
Purpose of HEAP	The purpose of the HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated SAP, and it should be read in conjunction with them.
Trial protocol version; date	This document has been written based on information contained in the trial protocol version 9, 04/02/2019
Trial Statistical Analysis Plan (SAP) version, date	2.2, 11/06/2019
Trial HEAP version, date	1.0, 01/04/2020
HEAP revisions	n/a
Roles and responsibilities	The HEAP was drafted by Dr Aideen Ahern (Junior HE: who has since left) and finalised and approved by Dr Sian Noble (Senior HE). The trial health economists Shaun Harris and Sian Noble are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	Name	*Signature*	Date
Lead Health Economist	Dr Sian Noble		23/06/2020
Chief Investigator	Professor Rachael Gooberman-Hill		23/06/2020

1.2 Glossary of terms and abbreviations

BPI	Brief Pain Inventory
HCHSI	Hospital and Community Health Services Index
HE	Health Economist
HEAP	Health Economics Analysis Plan
ICECAP-A	ICEpop CAPability measure for Adults
ICER	Incremental Cost-Effectiveness Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
MAR	Missing At Random
MI	Multiple Imputation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	Net Monetary Benefit
OKS	Oxford Knee Score
PMM	Predictive mean matching
PSS	Personal Social Services
QALYs	Quality Adjusted Life Years
SAP	Statistical Analysis Plan
SD	Standard Deviation
STAR	Support for treatment after joint replacement
UK	United Kingdom
WTP	Willingness-to-pay

Section 2: Trial introduction and background

2.1 Trial background and rationale

Total knee replacements aim to reduce pain, functional limitations and associated disability for those suffering from osteoarthritis. In the United Kingdom (UK) over 100,000 total knee replacements were performed in 2015[1 2] and approximately 20% of patients experience chronic pain after total knee replacement[3]. There is little evidence for interventions for the management of this pain, and current healthcare provision is patchy and inconsistent. Given the complexity of this condition, multimodal and individualised interventions matched to pain characteristics are needed. To improve the management of chronic pain after total knee replacement, the STAR (Support and Treatment After joint Replacement) care pathway was developed[4]. The aim of this multi-centre randomised controlled trial is to evaluate the clinical and cost-effectiveness of the care pathway for patients with chronic pain after total knee replacement.

2.2 Aim of the trial

Briefly, the STAR trial aims to evaluate the clinical effectiveness of a new care pathway when compared with usual care for people with chronic pain after knee replacement.

2.3 Objectives of the trial

The primary objective of the trial is to assess whether there is a clinically important difference, using the Brief Pain Inventory (BPI) pain score, of a new care pathway when compared with usual care for people with chronic pain after knee replacement.

2.4 Trial population

Inclusion criteria: Patients aged 18 years and over who have received a primary total knee replacement because of osteoarthritis at a participating National Health Services (NHS) Trust and who report pain in their operated knee at 2–3 months after surgery (score of 0–14 on the Oxford Knee Score (OKS) pain subscale[5]).

Exclusion criteria: A lack of capacity to provide informed consent to participate, previous participation in the STAR trial for the contralateral knee, participation in another research study that interferes unacceptably with the STAR trial. Patients unable to complete study questionnaires in English or Welsh, and those unable to be contacted by telephone.

2.5 Intervention and comparator

Intervention: one-hour STAR assessment clinic with an Extended Scope Practitioner to identify potential causes of pain and enable onwards referral to appropriate existing services. Up to 6 telephone follow-up calls from the Extended Scope Practitioner over the 12-month follow-up period.

Comparator: care as usual as provided by the patient's hospital consisting of either routine follow-up only at six weeks post-operative. One centre provides an additional three-month appointment. All centres provide additional follow-up with a surgeon if requested but do not include follow-up by practitioners specialising in pain.

2.6 Trial design

This is a pragmatic, parallel, two-arm, multi-centred randomised controlled trial using 2:1 intervention: control randomisation, with an internal pilot phase and embedded economic evaluation and qualitative studies. The trial is currently taking place at 8 NHS secondary care centres across the UK.

2.7 Trial start and end dates

Recruitment started in October 2016 and is due to finish July 2019. The follow-up period will run for 12 months until July 2020.

Section 3: Economic approach

3.1 Aim of economic evaluation

The health economic analysis with consist of a within-trial analysis of the cost-effectiveness of a new care pathway for patients with long-term pain after knee replacement.

3.2 Objectives of economic evaluation

The primary objective of the health economic evaluation is to estimate the short-term cost-effectiveness of The STAR pathway compared to usual care.

3.3 Overview of economic analysis

The within trial economic analysis from both an NHS and PSS and wider perspective (to include patient costs) will be performed using individual patient level data from the STAR trial. The primary economic analysis will compare the difference in NHS and PSS costs relating

to the treatment of long-term pain with the difference in QALYS. Wider societal costs including opportunity costs incurred by the patient or family members will not be included within the cost-effectiveness analysis.

3.4 Jurisdictions

The trial is conducted in the UK, which has a National Health Services (NHS), providing publicly funded healthcare, primarily free of charge at the point of use.

3.5 Perspective

The primary cost-effective analysis will take an NHS and Personal Social Services (PSS) perspective. A secondary analysis will take a broader perspective to include patients' costs.

3.6 Time horizon

The primary economic analysis will compare the costs and effects of each arm 12 months after randomisation.

Section 4: Economic data collection and management

4.1 Statistical software

Stata version 15.1 or higher will be used for all economic analyses.

4.2 Identification of resources

Only resources used in relation to chronic pain on the operated knee will be measured from randomisation to 12 months follow-up. The following items of resource use that may differ between arms will be measured: resources used in relation to the intervention, health service resource use, personal social services and personal expenditure related to the chronic pain and its treatment e.g. travel, non-prescribed medications, special equipment.

4.3 Measurement of resource use data

The costs relating to the intervention will be determined by calculating the costs of staff time and any resources and materials used in providing the STAR treatment pathway. This includes any resources associated with training, delivery and administration for face-to-face assessments and telephone contacts, but excludes any costs associated with research which would not be a component of the delivery of the STAR intervention in a standard clinical setting. Resources used will be recorded on a standardised proforma.

Resource use data including inpatient stays and outpatient visits for all patients at the treating hospitals will be obtained from hospital electronic systems. Use of health services including primary and community care, use of personal social services and additional costs will be collected in the participant completed follow-up questionnaires at 6 and 12 months after randomisation. Participants can choose to complete a paper or an online version and will receive a questionnaire through the post or an email link as appropriate. Participants are provided with resource diaries and prescribed medication folders to prospectively record and document any health resources they have used, to assist them in the completion of the questionnaires.

4.4 Valuation of resource use data

All resources will be valued in monetary terms using appropriate UK unit costs or participant valuation estimated at the time of analysis. NHS reference costs will be employed to value hospital resource use and intervention costs. Medications will be valued using the British National Formulary (BNF) or Prescription Cost Analysis (PCA) for England. Primary Care consultations and any other community-based health care services will be mainly costed using Curtis 'Unit Costs of Health & Social Care[6]. Costs directly reported in the Resource Use Questionnaires will be used to value out-of-pocket expenditures related to the patient's urinary symptoms and any associated treatment (e.g. over the counter medications). Paid time off work will be costed using the Office of National Statistics (ONS) information on salaries. (see Table 1 for more details)

When a unit cost is not available for the year of analysis, an upgrade will be made using the appropriate method of inflation (e.g. NHS cost inflation index (NHSCII)).

4.5 Identification of outcomes

The primary economic outcome measure will be the Quality Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L[7] quality of life instrument. Secondary outcomes for the economic evaluation will include the effectiveness co-primary outcomes of BPI pain score and OKS in addition to ICEpop CAPability measure for Adults (ICECAP-A)[8] and the Short Form-12 (SF-12)[9].

4.6 Measurement of outcomes

Outcomes will be collected at baseline, 6- and 12- months post randomisation. using a participant self-completed questionnaire, which can be completed online or on paper, using a postal questionnaire or an email link as appropriate.

4.7 Follow-up of non-responders

Participants who have not returned their questionnaires after their two-week reminder are offered the option of completing the questionnaires over the phone, and in some cases are offered a home visit. Telephone calls to patients who do not return a follow-up questionnaire will be performed by a researcher from a different trial centre to ensure that the researcher is blinded to treatment allocation

4.7 Valuation of outcomes

Utility values will be derived from response to the EQ-5D-5L. They will be derived using the approach recommended by National Institute for Health and Care Excellence (NICE)[10]. NICE currently advises that the 5-level valuation set for England is not recommended for use to derive utilities, instead advising that the validated mapping function to the 3-level valuation set be used for reference-case analysis. These will be used to form QALYs over the 12-month period, adjusting for any imbalances in baseline EQ-5D-5L scores.

Section 5: Economic data analysis

5.1 Analysis population

It is intended that all participants randomised into the trial will be analysed as per their randomisation group in accordance with a modified intention to treat (ITT) principle (i.e. all randomised participants who provided outcome data).

5.2 Timing of analyses

The primary analysis will be conducted once all patients have been followed up for 12 months from randomisation

5.3 Discount rates for costs and benefits

There will be no discounting of costs or effects given the 1-year duration of the study.

5.4 Cost-effectiveness threshold

The primary economic analysis will use a cost-effectiveness threshold of £20,000 per QALY[11].

5.5 Data cleaning for analysis

Face validity tests will be conducted on data (e.g. to identify misspelt text) and checked against the source documents. Corrections identified will be documented in the Stata code.

5.6 Missing data

Missing data may relate to item non-response, where a questionnaire is partially incomplete, or unit non-response where all the information is missing.

Item non-response on the EQ-5D-5L™ questionnaire will not be individually imputed; instead the questionnaire will be treated in the same manner as those which are fully incomplete with QALYs imputed with unit non-response procedures (e.g. multiple imputation).

Baseline covariates will be imputed in accordance with the statistical analysis. Imputation at baseline will allow for all participants to be included in the analysis of the outcome score; simple imputation methods are considered superior when baseline values are included in an adjusted analysis to improve the precision of the treatment effect (White and Thompson, 2005). This imputation will only be considered for the regression analysis and not for summarising baseline scores.

The resource use questionnaire asks patients to record the health services they have used and anything they have had to buy directly because of the pain they have experienced in their replaced knee. It consists of five sections: use of health care services, travel to services, use of medications, home changes and home care, and time off work. Item non-response within this questionnaire may represent either the individual failing to record a non-zero value, or alternatively left incomplete to represent no contact. For each part, if one or more questions are at least partially complete, any fully incomplete questions will be assumed to represent no contact or usage of that type.

The pattern of missing outcome and resource data, after implementation of item-non-response procedures outlined above, will be examined. The appropriate method for dealing with missing data will depend on the prevalence of missing data and likely mechanism of missingness. If the data is missing at random (MAR)[12](missingness dependent upon observed

data but not the unobserved outcomes), multiple imputation using chained equations will be used to impute missing items to provide an unbiased analysis on all randomised individuals. Imputations will be combined following Rubin's rules (Rubin, 1987). Due to the predefined range of outcome scores, including utility derived from the EQ-5D-5L™ and the typically skewed distribution of costs data, predictive mean matching (PMM) will be used to ensure imputed values are consistent with observed data. The plausibility of the MAR assumption will be explored by comparing observed data in participants with and without the item of interest and further sensitivity analyses will explore the robustness of conclusions should outcomes be assumed to be missing not at random (MNAR).

5.7 Analysis of costs

The mean resource use and costs will be estimated and presented by trial arm for each resource use category (e.g. outpatient visits, medication use, etc.). Standard deviations (SD) and the number of patients included in each category by arm will also be presented. Appropriate regression techniques e.g. SUR will be used to estimate adjusted mean costs and the difference in adjusted mean costs (and their associated 95% confidence intervals) between the trial arms in relation to NHS and PSS costs and in relation to NHS, PSS and patient costs. The regression will be adjusted for the minimisation variables of the randomisation process (the Brief Pain Inventory Severity and Interference Scales), and the stratification variable (orthopaedic centre).

5.8 Analysis of outcomes

The primary economic outcome in STAR is the QALY. QALYs for each patient over the 12-month period will be calculated from the utility values using the area under the curve approach, and this will consider any deaths that have occurred during the duration of the study.

Appropriate regression techniques e.g. SUR will be used to estimate adjusted mean QALYs and the difference in adjusted mean QALYs (and their associated 95% confidence intervals) between the trial arms. The regression will be adjusted for baseline utility, the minimisation variables of the randomisation process (the Brief Pain Inventory Severity and Interference Scales), and the stratification variable (orthopaedic centre).

BPI pain score, OKS, ICECAP-A and SF-12 which will be used for the cost-consequence analysis will be estimated as outlined in the SAP.

5.9 Analysis of cost-effectiveness

Primary Economic analysis (NHS and PSS perspective) and Secondary Economic analysis (NHS, PSS, and patient perspective)

Taking each perspective in turn, if neither intervention is dominant (i.e. less expensive and more effective), incremental cost-effectiveness ratios will be created using the outputs from the appropriate regression. These outputs will also be used to estimate the incremental net monetary benefit (INMB) statistic at the standard NICE willingness to pay threshold of £20,000 per QALY.

Cost-consequence analysis

A cost consequence analysis will be conducted in which mean adjusted costs and outcomes (OKS, BPI pain score, ICECAP-A and SF-12) are displayed in tabular form.

5.10 Subgroup analyses

Analyses will also be conducted on the final dataset to investigate how cost-effectiveness varies between different patient subgroups. Three subgroup analyses will be conducted.

1) An analysis on the primary economic outcome from the NHS and PSS perspective will be performed by including appropriate interaction terms between the intervention group and other patient characteristics in the regression models, to investigate any differential effects in certain subgroups of the population. These factors will be trial centre and baseline Oxford Knee Score.
2) An analysis will be performed for those sites who limit patients who are less than 1 hour drive away versus those who accept all patients regardless of the distance from site.

3) An analysis will be performed in which patients who completed follow-up prior to March 23rd 2020 (the start of the UK lockdown due to Covid-19) will be compared to those who completed follow-up on or after this date.

5.11 Sampling uncertainty

Uncertainty will be addressed using cost-effectiveness acceptability curves for a range of willingness-to-pay thresholds. For multiple feasible WTP thresholds, the probability of cost-effectiveness will be explicitly highlighted.

5.12 Sensitivity analyses

Sensitivity analyses will be undertaken to explore methodological uncertainty in the economic evaluation. Issues may arise in the cleaning and analysis which may mean more analyses than the one specified will be included.

The results for complete cost and quality of life data (i.e. those with no missing data) will be provided to identify the impact of missing data on the analysis.

Section 6: Reporting/publishing

6.1 Reporting standards

CHEERS guidelines[15] will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers.

6.2 Deviations from the HEAP

Any deviation from HEAP will be described and justified in the final published report.

Table 1 Resource use sources

Resource	Source of cost
NHS inpatient stays	NHS reference costs
Outpatient visits	NHS reference costs
A& E visits/admissions	NHS reference costs
Intervention appointment and phone calls	NHS reference costs & Lesley Curtis PSSRU
Prescriptions	British National Formulary/ Prescription Costs Analysis England
Appointment with a GP at the GP practice	Lesley Curtis PSSRU
Home visit with a GP	Lesley Curtis PSSRU
Telephone call with a GP	Lesley Curtis PSSRU
Appointment with a GP practice nurse at the GP practice	Lesley Curtis PSSRU
Telephone call with a GP practice nurse	Lesley Curtis PSSRU
Home visit from a district nurse	Lesley Curtis PSSRU
NHS 111 or NHS direct Wales telephone call	Lesley Curtis PSSRU
Appointment with an NHS physiotherapist at a health centre/GP practice	Lesley Curtis PSSRU
Appointment with a private physiotherapist	Lesley Curtis PSSRU
Appointment for NHS acupuncture (**not** in a hospital)	Lesley Curtis PSSRU
Appointment for private acupuncture	web-based resources
Appointment for private hydrotherapy	web-based resources
Community-based urology service	Lesley Curtis PSSRU
Other NHS community care visit	Lesley Curtis PSSRU
Paid time off work	Office of National Statistics (ONS)
Home changes and home care	Patient self-reported, web-based resources
Home care worker	Patient self-reported, Lesley Curtis PSSRU
Over the counter medication	Patient self-reported, web-based resources
Other expenses	Patient self-reported, web-based resources
Travel costs	Patient-reported

Table 2 Example of how resource use may be presented

Resource category	Intervention N= XX			Usual Care N=XX		
	N	Mean resource use (SD)	Mean cost (£) (SD)	N	Mean resource use (SD)	Mean cost (£) (SD)
Intervention appointment (number)						
Intervention phone calls (number)						
Inpatient stays (number of nights)						
Outpatient appointments (number of appointments)						
A&E visits/admissions (number of admissions)						
Appointment with a GP at the GP practice (number of appointments)						
Home visit with a GP (number of visits)						
Telephone call with a GP (number of calls)						
Appointment with a GP practice nurse at the GP practice (number of appointments)						
Telephone call with a GP practice nurse (number of calls)						
Home visit from a district nurse (number of visits)						
NHS 111 or NHS Direct Wales telephone call (number of calls)						
Appointment with an NHS physiotherapist at a health centre/GP practice (number of appointments)						
Appointment with a private physiotherapist (number of appointments)						
Appointment for NHS acupuncture (number of appointments)						
Appointment for private acupuncture (number of appointments)						
Appointment for private hydrotherapy (number of appointments)						
Other primary or community care contacts (number of contacts)						
Prescriptions (number of prescriptions)						
Home care worker (number of hours)						
Paid Time off work (number of hours)						
Travel costs (number of journeys)						

Over-the-counter medication (number of medications)						
Any other costs (number of items)						

Table 3. Example of how the main economic analyses may be presented

Allocation arm	N	Adjusted cost (£) mean (95% CI)	Adjusted QALY mean (95% CI)	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (£/QALY)	NMB (£) at £20000/QALY (95% CI)
NHS and PSS Costs							
Intervention							
Usual Care							
Patient Costs							
Intervention							
Usual Care							
Total Costs							
Intervention							
Usual Care							

Table 4. Example of how the Cost consequence analysis may be presented

Variable	N (I:UC)	Adj. Intervention Mean (95% C.I.)	Adj. Usual Care Mean (95% C.I.)	Adj. difference in means (95% C.I.)
QALY				
BPI				
OKS				
ICECAP-A				
SF-12				
NHS & PSS costs				
Patient costs				
Total costs				

(I=Intervention, UC=Usual Care)

Table 5. Example of how the economic sensitivity analyses maybe presented

Allocation arm	N	Adjusted cost (£) mean (95% CI)	Adjusted QALY mean (95% CI)	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (£/QALY)	NMB (£) at £20000/QALY (95% CI)
Sensitivity Analyses 1: Different ways of dealing with missing data							
Intervention							
Usual Care							
Sensitivity Analyses 2: Complete Case/Imputed							
Intervention							
Usual Care							
Sensitivity Analyses 3: XXX							
Intervention							
Usual Care							
Sensitivity Analyses 4: XXX							
Intervention							
Usual Care							

(Above are examples, repeat as many times number of sensitivity analyses performed)

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